

1,169,944



PATENT SPECIFICATION

L169,944

NO DRAWINGS

Inventor: GERAINT JONES

Date of filing Complete Specification: 11 July, 1967.

Date of Application (No. 38195/66): 25 Aug., 1966.

Complete Specification Published: 5 Nov., 1969.

Index at acceptance:—C2 C(1H1A3, 1H1C2, 1Q2, 1Q3, 1Q6B1, 1Q7A, 1Q8A, 1Q8C, 1Q9C, 1Q9F2, 1Q11D, 1Q11J, 2A2, 2A5, 2A14, 2R17, 22Y, 220, 226, 227, 29Y, 29X, 30Y, 304, 32Y, 323, 36Y, 364, 650, 662, 682, 790, LF)

International Classification:—C 07 c 87/28, 93/14

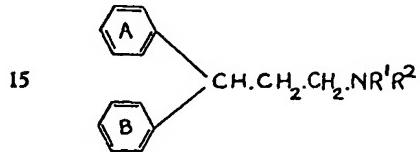
COMPLETE SPECIFICATION

Novel 3,3-Diphenylpropylamines and processes for the preparation thereof

We, ED. GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE, a body corporate organised and existing under the laws of Switzerland, of 6110, Wolhusen, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

- 10 This invention relates to new 3,3-diphenylpropylamine derivatives which have antidepressant activity.

According to the invention we provide alkane derivatives of the formula:—



wherein R¹ stands for hydrogen or an alkyl radical, and R² stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, and acid-addition salts thereof, provided that, when A stands for the phenyl radical and B stands for the 4-methylphenyl or 4-methoxyphenyl radical, R¹ and R² do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R¹ and R² do not both stand for the ethyl radical.

As a suitable value for R², or for R¹ when it stands for an alkyl radical, there may be mentioned, for example, an alkyl radical of

not more than 6 carbon atoms and more particularly an alkyl radical of not more than 2 carbon atoms, for example the methyl radical.

The substituent(s) which may be present in the phenyl radical A may, for example, be selected from fluorine and chlorine atoms, and the trifluoromethyl radical. The substituent(s) which is or are present in the phenyl radical (B) may, for example, be selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms, for example the methyl and methoxy radical.

Preferred compounds of the invention are those wherein R¹ stands for hydrogen or the methyl radical, R² stands for the methyl or ethyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and the trifluoromethyl radical.

As specific alkane derivatives of the invention there may be mentioned, by way of example, N,N-dimethyl-3,3-bis-(4-fluorophenyl)propylamine, N,N-dimethyl-3-(4-fluorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(4-chlorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(3-fluorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(2-methylphenyl)-3-phenylpropylamine, N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, N,N-dimethyl-3-(3-fluorophenyl)-3-phenylpropylamine, N,N-dimethyl-3-(4-chlorophenyl)propylamine, N,N-dimethyl-3-(4-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(3-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(4-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(3-methyl-4-fluorophenyl)propylamine, N,N-dimethyl-3,3-bis-(3-trifluoromethylphenyl)propylamine and N,N-

35

40

45

50

55

60

65

70

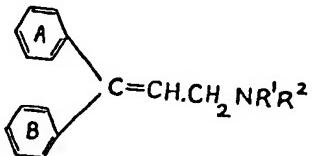
75

[Price 4s. 6d.]

dimethyl - 3 - (3 - trifluoromethylphenyl)-3 - phenylpropylamine, and acid-addition salts thereof.

- 5 As suitable acid-addition salts there may be mentioned salts derived from inorganic or organic acids affording pharmaceutically-acceptable anions, for example hydrochlorides, oxalates, citrates, maleates or tartrates.

10 According to a further feature of the invention we provide a process for the manufacture of the alkane derivatives of the invention, which comprises reducing an alkene derivative of the formula:—

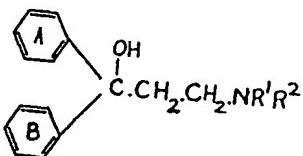


- 15 wherein A, B, R' and R^2 have the meanings stated above, or an acid-addition salt thereof.

The reduction may be carried out, for example, by catalytic hydrogenation, for example by hydrogenation in the presence of a palladium-on-carbon catalyst.

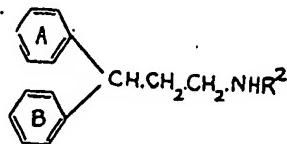
20 The hydrogenation may be carried out in an inert diluent or solvent, for example ethanol, and it may be carried out at ambient temperature or under the influence of heat, and at atmospheric or an elevated pressure. Alternatively, for example, the reduction may be carried out by the interaction of the alkene derivative with red phosphorus and hydriodic acid. In this case the alkene derivative may conveniently be formed *in situ* by interaction of the corresponding tertiary alcohol with red phosphorus and hydriodic acid.

25 The alkene derivatives used as starting materials in the above process (some of which are described and claimed in our co-pending Application No. 8165/66 (Serial No. 1134715) may be obtained by dehydrating the corresponding hydroxy compounds of the formula:—

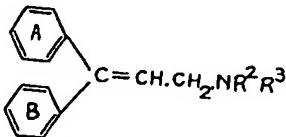


- 30 wherein A, B, R' and R^2 have the meanings stated above, or an acid-addition salt thereof, by the interaction thereof with hydrochloric acid in the presence of a diluent or solvent, for example acetic acid.

35 According to a further feature of the invention we provide a process for the manufacture of those of the alkane derivatives of the invention which are of the formula:—



wherein A, B and R^2 have the meanings stated above, and acid-addition salts thereof, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R^2 have the meanings stated above, and R^2 stands for a hydrogenolysable group, or an acid-addition salt thereof.

As a suitable value for R^2 there may be mentioned, for example, the benzyl radical. The hydrogenolysis may be carried out by catalytic hydrogenation using the reactants and conditions described above.

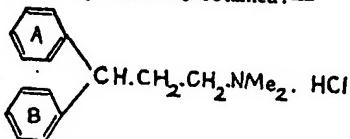
The starting materials in the last-named process may be obtained by the general dehydration process outlined above.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1

5 Parts of N,N - dimethyl - 3,3 - bis - (4-fluorophenyl)prop-2-enylamine hydrochloride are dissolved in 20 parts of dry ethanol. 2.5 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10%, in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated to a small volume. Dry ether is slowly added until crystallisation begins, and 500 parts of dry ether are then added. The mixture is filtered and the solid residue is washed with dry ether and then dried. The solid is crystallised from ethyl acetate containing a trace of ethanol, and there is thus obtained N,N-dimethyl-3,3 - bis - (4 - fluorophenyl)propylamine hydrochloride, m.p. 188—189°C.

In a similar manner, using the appropriate alkene derivative as starting material, the following compounds are obtained:—



50

60

65

70

75

80

85

90

10

15

20

25

30

35

A	B	m.p. (°C.)	Crystallisation solvent(s)
Ph	4-F-Ph	141-144	n-butyl acetate
Ph	4-Cl-Ph	154-157	ethyl acetate—trace of ethanol
Ph	3-F-Ph	166-168	"
Ph	2-Me-Ph	165-167	"
Ph	2-MeO-Ph	166-167	"
Ph	3-CF ₃ -Ph	145-148	ethyl acetate—petroleum ether (b.p. 60-80°C.)
4-Cl-Ph	4-Cl-Ph	193-196	n-butyl acetate
4-Cl-Ph	4-F-Ph	173-176	n-butyl acetate
3-F-Ph	3-F-Ph	178-180	ethyl acetate—trace of ethanol
3-CF ₃ -Ph	3-CF ₃ -Ph	158-160	ethyl acetate—petroleum ether (b.p. 60-80°C.)

The N,N - dimethyl - 3,3 - bis-(4-fluorophenyl)prop - 2 - enylamine hydrochloride used as starting material in the process described above may be obtained as follows:—

A mixture of 6 parts of N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine (m.p. 120°C.), 50 parts of acetic acid and 15 parts of 10N-hydrochloric acid is heated at 100°C. for 3 hours. The reaction mixture is evaporated to small volume and the residual oil is dissolved in water. The solution is washed with ether and is then made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and an ethereal solution of hydrogen chloride is then added to the extract until the precipitation of solid is complete. The precipitated solid is collected by filtration and is then crystallised from butyl acetate. There is thus obtained N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, m.p. 209°C.

The N, N - dimethyl - 3,3 - bis - (4-fluorophenyl) - 3 - hydroxypropylamine used as starting material can be obtained in conventional manner by the interaction of the appropriate Grignard reagent with the appropriate ketone.

The alkene derivatives used as starting materials for the preparation of the alkane derivatives listed in the above table may be obtained in similar manner to that described for N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)prop - 2 - enylamine hydrochloride.

EXAMPLE 2

6 Parts of N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride are dissolved in 30 parts of dry ethanol. 3 Parts of 5% palladium-on-carbon catalyst are added, and the mixture is shaken in an atmosphere of hydrogen at ambient temperature and atmospheric pressure. When the absorption of hydrogen has ceased (approximately 10% in excess of the calculated volume is absorbed), the catalyst is removed by filtration and the filtrate is evaporated. The residue is dissolved in 50 parts of water, and the solution is basified with ammonia. The base is extracted twice, each time with 100 parts of ether, and the combined ethereal extracts are dried with anhydrous magnesium sulphate. To the dry ethereal solution there is added an ethereal solution of oxalic acid until precipitation is complete. The mixture is filtered, and the solid residue is washed with ether and then dried on the filter. The solid is crystallised from ethanol, and there is thus obtained N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine oxalate, m.p. 187-190°C.

The N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine hydrochloride used as starting material may be obtained as follows:—

A mixture of 58.3 parts of N - benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine, 465 parts of acetic acid and 117 parts of 10N-hydrochloric acid is heated under reflux for 0.5 hour. The mixture is evaporated to small volume and the residual oil is dissolved in water. The solution

40

45

50

55

60

65

70

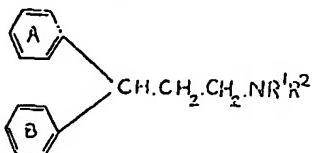
75

is made strongly alkaline by the addition of 2N-aqueous sodium hydroxide and is then extracted with ether. The ethereal extract is dried over anhydrous calcium sulphate and is 5 evaporated *in vacuo*. The residual oil is fractionally distilled at a pressure of 0.2mm Hg. and the fraction having b.p. 172-178°C. is collected. There is thus obtained N - benzyl - 10 N - methyl - 3,3 - bis - (4 - fluorophenyl) - prop - 2 - enylamine, which may be converted into the hydrochloride (m.p. 132°C.) by conventional means.

N - Benzyl - N - methyl - 3,3 - bis - (4 - fluorophenyl) - 3 - hydroxypropylamine 15 can be obtained in conventional manner by the interaction of ethyl 3 - (N - benzyl - N - methylamino)propionic acid and the appropriate Grignard reagent.

WHAT WE CLAIM IS:—

20 1. An alkane derivative of the formula:—



25 wherein R¹ stands for hydrogen or an alkyl radical, and R² stands for an alkyl radical, and the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from halogen atoms and trifluoromethyl, alkyl and alkoxy radicals, or an acid-addition salt thereof, provided that, when A stands for the phenyl radical and B stands for the 4 - methylphenyl or 4 - methoxyphenyl radical, R¹ and R² do not both stand for the methyl radical, and, when A stands for the phenyl radical and B stands for the 4-methylphenyl radical, R¹ and R² do not both stand for the ethyl radical.

30 2. A compound as claimed in claim 1 wherein R¹ stands for hydrogen or an alkyl radical of not more than 6 carbon atoms, R² stands for an alkyl radical of not more than 6 carbon atoms, and the phenyl radical A optionally bears one or two substituents selected from fluorine and chlorine atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents selected from fluorine and chlorine atoms, the trifluoromethyl radical, and alkyl and alkoxy radicals of not more than 3 carbon atoms.

35 3. A compound as claimed in claim 1 wherein R¹ stands for hydrogen or the methyl radical, R² stands for the methyl or ethyl radical, the phenyl radical A optionally bears one or two substituents selected from halogen atoms and the trifluoromethyl radical, and the phenyl radical B bears one or two substituents

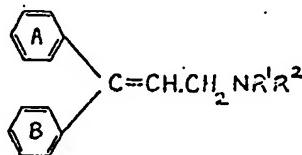
selected from halogen atoms and the trifluoromethyl radical.

4. A compound as claimed in claim 3 wherein the halogen substituent(s) present in 60 phenyl radical B, and optionally present in phenyl radical A, is or are selected from fluorine and chlorine atoms.

5. A compound selected from N,N - dimethyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3 - (4 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (4 - chlorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (3 - fluorophenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2-methylphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3 - (2 - methoxyphenyl) - 3 - phenylpropylamine, N,N - dimethyl - 3,3 - bis - (4 - chlorophenyl) - propylamine, N,N - dimethyl - 3 - (4-chlorophenyl) - 3 - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3-fluorophenyl) - propylamine, N - methyl - 3,3 - bis - (4 - fluorophenyl)propylamine, N,N - dimethyl - 3,3 - bis - (3 - trifluoromethylphenyl)propylamine and N,N - dimethyl - 3 - (3 - trifluoromethylphenyl) - 3 - phenylpropylamine, and acid-addition salts thereof.

6. An acid-addition salt as claimed in any of claims 1 to 5 which is a hydrochloride, 85 oxalate, citrate, maleate or tartrate.

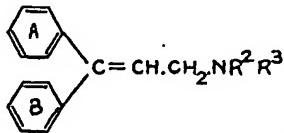
7. A process for the manufacture of a compound claimed in any of claims 1 to 6, which comprises reducing an alkene derivative of 90 the formula:—



wherein A, B, R¹ and R² have the meanings stated in claim 1, or an acid-addition salt thereof.

8. A process as claimed in claim 7 in which the reduction is carried out by hydrogenation in the presence of a palladium-on-carbon catalyst.

9. A process for the manufacture of a compound claimed in claim 1 wherein R¹ stands for hydrogen, which comprises hydrogenolysing a compound of the formula:—



wherein A, B and R² have the meanings stated above, and R³ stands for a hydro-

genolysable group, or an acid-addition salt thereof.

5 10. An alkane derivative, claimed in claim 1, substantially as described in either of the foregoing Examples.

11. A process for the manufacture of an

alkane derivative, claimed in claim 7 or 9, substantially as described in either of the foregoing Examples.

B. F. DREW,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.